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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/738,423 | 12/16/2003 | Ivan C. King | 873-Z-US | 8783 |

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| EXAMINER | |
|---|---|
| LI, QIAN JANICE | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

DATE MAILED: 07/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/738,423 | KING, IVAN C. | |
| | Examiner | Art Unit | |
| | Q. Janice Li, M.D. | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *100-112* is/are pending in the application.

4a) Of the above claim(s) *101,102,104, 105, 107,109 and 110* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *100,103,106, 108,111 and 112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of Group I, drawn to a method of using an attenuated tumor-targeted bacteria, and species election drawn to Salmonella and cisplatin is acknowledged. The traversal is on the ground(s) that the claims have as a common feature, attenuated tumor-targeted bacteria, and that a search of these claims can be made without serious burden. This is not found persuasive. Claims of Group II are directed to using an attenuated tumor-targeted bacteria as a vector to deliver one or more nucleic acid(s) encoding various effector molecules, whereas claims of group I are directed to treating tumor with an attenuated bacteria, and do not require additional effector molecules. The inventions are mutually exclusive and independent methods for treating cancer. As such; the Invention of group II requires different reagents, steps, protocols, and technical considerations than the Invention of group I. The searches for groups II and I would have certain overlap, but they are not co-extensive. In an art with abundant literatures such as instant one, it would impose a serious search burden on the Office. Thus it is maintained that each of the Inventions requires a separate search status and consideration. M.P.E.P. states, "FOR PURPOSES OF THE INITIAL REQUIREMENT, A SERIOUS BURDEN ON THE EXAMINER MAY BE PRIMA FACIE SHOWN IF THE EXAMINER SHOWS BY APPROPRIATE EXPLANATION OF SEPARATE CLASSIFICATION, OR SEPARATE STATUS IN THE ART, OR A DIFFERENT FIELD OF SEARCH AS DEFINED IN MPEP § 808.02". Therefore, it is maintained that these

inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive, as indicated by the separate classifications. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 100-112 are pending, however, claims 101, 102, 104-107, 109, 110 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 100, 103, 106 108, 111, 112 are under current examination.

***Priority***

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the

invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In the instant case, the disclosure of the prior-filed applications, Application No. 09/645415, and provisional applications, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The disclosures of aforementioned prior applications are drawn to using an attenuated tumor-targeted bacteria as a carrier to deliver one or more nucleic acids encoding various effector molecules to tumors, which requires the presence of the effector moleculues, not treating cancer with an attenuated tumor-targeted bacteria alone. Thus, the priority date for instant claimed subject matter has been established as instant filing date, i.e. December 16, 2003.

Applicant is invited to specifically point out where in the priority document, the support for instantly claimed subject matter can be found.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 100, 103, 106, 108, 111, 112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim limitation, "attenuated tumor-targeting" bacteria. The specification fails to define what structure is required for a bacterium to possess that would meet claim limitation, particularly for the term "tumor-targeting", and thus the metes and bounds of the claims are unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 100, 103, 106, 111, 112 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the growth of a solid tumor cancer comprising administering to a subject in need an effective amount of one or more chemotherapeutic agents, supplemented with a msbB$^-$ *Salmonella* mutant (having genetically modified bacterial lipid A), does not reasonably provide enablement for inhibiting the growth of a solid tumor cancer supplemented with the genus of attenuated tumor-targeted bacteria. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These

factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are drawn to using a genus of bacteria that are attenuated in toxicity and capable of tumor targeting. The specification teaches genetically engineered [on the lipid composition of] *Salmonella* have been demonstrated to be capable of tumor targeting, possess anti-tumor activity and are useful in delivering effector genes such as the herpes simplex thymidine kinase to solid tumors (Specification, § 2.8, paragraph 0040). Although the specification cited numerous prior art teaching that modification on lipid A pathway may reduce the ability of *E coli* bacteria to stimulate production of TNF-α (Specification, § 2.9), and thus reduce toxic effect to the host, the msbB$^-$ *Salmonella* mutant is the only bacterium taught in the specification to have tumor-targeting effect. The skilled artisan intending to practice the invention would have required to carry out undue experimentation to find out for themselves what the genus of "attenuated tumor-targeting" bacteria embraces.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the

invention commensurate with the scope of the claims without undue experimentation.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 100, 103, 106, 108, 111, 112 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Low et al* (Nat Biotech 1999;17:37-41, IDS), in view of *Schachter et al* (Cancer Biother Radiopharm 1998 Jun;13:155-64).

*Low et al* teach a method of treating tumor using a strain of *Salmonella* having disruption in msbB gene (msbB$^-$ mutant), said disruption reduces TNF-$\alpha$ induction (attenuated) and increases the $LD_{50}$ of this pathogenic bacterium by 10,000-fold. The mutant *Salmonella* retains its tumor-targeting properties, i.e. exhibiting tumor accumulation ratios in excess of 1000:1 compared to normal tissues. Administration of the bacteria to mice bearing melanoma results in

tumors that are less than 6% the size of tumors in untreated controls (e.g. fig. 4). The teaching of *Low et al* differs from instant claims in that it does not explicitly teach combining the bacteria therapeutic regimen with a chemotherapeutic agent such as cisplatin, or using such in humans.

*Schachter et al* supplemented *Low et al* by establishing a routine chemotherapeutic regimen in treating human melanoma using cisplatin, and that it was well known in the art to combine a chemotherapeutic regimen with a biotherapy in treating solid tumors such as melanoma. *Schachter et al* presented a chemo-biotherapy protocol for patients with metastatic melanoma by including cytokines that regulate patients' immune system with conventional chemotherapy. The rationale for the design of the combined therapy was to achieve a higher percentage of a complete response (CR, meaning disappearance of all measurable disease) to drug treatment. *Schachter et al* teach that conventional chemotherapy such as a 4-drug regimen (BCNU, DTIC, **cisplatin** and tamoxifen) could have 40-50% response rate in patients being treated, but only 10-14% of patients achieved a complete response. When using the chemo-biotherapy, the response rate was 50%, and the complete response rate was up to 22%. *Schachter et al* do not specifically teach the tumor-targeted bacteria, but illustrated the need of further improvement of the conventional chemotherapy.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the attenuated tumor-targeted mutant *Salmonella* therapy as taught by *Low et al* with a routine chemotherapy

regimen as taught by *Schachter et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention for maximal therapeutic effects. Given the state of the art that the conventional therapy alone was often insufficient in treating cancer, given the skilled was constantly searching for new means to improve cancer treatment, and given that each of the cited references teaches an agent that is effective in cancer therapy, one would have had a reasonable expectation of success when combining the two. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **William Phillips**, whose telephone number is (571) 272-0548.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is **(866) 217-9197**. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

*QJL*
July 6, 2006